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Endocrinopathy of chronic cystic mastitis

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ENDOCRINOPATHY OF CHRONIC CYSTIC MASTITIS

BY

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INTRODUCTION

The purpose of this paper is to better acquaint the student with the ever changing views of investigators regarding Chronic Cystic Mastitis and the relationship of the endocrine glands.

For several years, widespread study has been directed toward the subject of Chronic Cystic Mastitis and this study has become more intensive since the mysteries of the endocrine system have been revealed along with the isolation and synthesis of the hormones, as well as the actions of some of these hormones determined with a great measure of accuracy.

The complexity of this subject renders its comprehension extremely difficult.

In preparing this paper I have aimed to elucidate upon, and to arrange the subject matter in the most orderly and comprehensive manner.

DEFINITION

Chronic Cystic Mastitis is a term commonly used to describe a condition of the breast characterized by abnormal hyperplasia. This condition has defied classification for a good many years and is therefore known by a multiplicity of names such as; Chronic Mastitis, Chronic Cystic Mastitis, Chronic Interstitial Mastitis, Diffuse Fibroadenoma, Involution Cysts, Abnormal Involution of the Breast, Cystic Disease of the Breast, Schimmelbusch's Disease, Mazoplasia, Adenosis, Cystiphorous Desquamative Epithelial Hyperplasia, etc.(1)

"It is not that the name itself is of such importance, but almost all of these names commit one to a definite theory. The first group suggests that the condition is inflammatory in nature, the second that it is neoplastic, and the third that it is a perversion of involution. The only real evidence in support of the inflammatory hypothesis is the presence of lymphocytic infiltration, and that is always found in involution. Nor can we admit that the condition is a neoplasm. There is no tumor--that is a fact from which we cannot get away. It is true that the epithelial hyperplasia may at times suggest a neoplastic

process, but the same may be said of the epithelial hyperplasia in goiter. Abnormal involution comes nearest what we want to express, but the fundamental factor is hyperplasia rather than involution. Abnormal hyperplasia would be a preferable term. Cystic disease of the breast has the great advantage of commiting one to no theory, but there may be no cysts; although common they are not essential."(2)

The question arises as to whether the term "Chronic Cystic Mastitis", which is so commonly found in the literature, should be discarded. It seems that the conception of the disease that is conveyed by the term is so inaccurate and misleading that it should be abondoned.(3)

This condition is characterized by two types of desquamative epithelial hyperplasia which are described by the terms: 1. Mazoplasia and 2. Cystiphorous Epithelial Hyperplasia.(3)

"Mazoplasia is that condition in which there is a certain type of desquamation of epithelial cells in the terminal ducts and their acini, accompanied by hyperplasia of the pericanalicular and periacinous connective tissue and often new formations of ducts and acini. The shed epithelial cells accumulate in

and may distend the ducts and acini, giving rise to diffuse pain, and if there is little or not any subcutaneous fat a generalized fine nodularity of the breast can be felt upon palpation. The formation of cysts does not belong to the state of mazoplasia. The biological activity of the epithelial cells ends in this form of desquamation and does not lead to the formation of cysts, papilloma or carcinoma. The only pathological state that can be directly traced to mazoplasia is the formation of fibroadenomata.(3)

Mazoplasia is almost universally present in some degree until the menopause, in normal breasts of all women who have borne children. The condition is also present during development and in the breasts of male and female infants at birth. It is present at puberty, pregnancy and in the less active parts of a breast during lactation. It is a physiological rather than a pathological process."(3)

By cystiphorous desquamative epithelial hyperplasia is meant that type of desquamative epithelial hyperplasia which ends in the formation of cysts."(3)

"Bloodgood(4), Semb(5), Cheatle and Cutler (3), have joined Schimmelbusch(6) in separating the

type of Chronic Cystic Mastitis in which epithelial hyperplasia predominates from that in which a few large cysts dominate the clinical and microscopic picture. All authors also agree in attributing the possibilities of malignant change to the adenomatous rather than to the cystic type of the disease, yet none have succeeded in definitely untangling the apparent microscopic and clinical overlap between the two conditions. All of these authors believe the two types of Chronic Cystic Mastitis were essentially two phases of the same disease and capable of progressing one into the other."(7)

HISTORY

A review of the literature on Chronic Cystic Mastitis reveals the state of confusion which prevailed for over a century regarding the nature of the disease process.

Before Cooper's time (1828) cysts of the breast were generally believed to be malignant tumors but in 1828, Cooper regarded the condition as benign. (8)

In 1831, Cooper(9) reported one form of Chronic Cystic Mastitis and was the first to describe the blue tint typical of the unopened cyst upon exposure. This blue tint cyst undoubtedly belongs to this category. At this time he recommended local removal of the cyst or simple opening of the cyst with a lancet and inserting a piece of linen to bring about adhesive inflammation.

The clinical aspect of the disease was well described in 1845, by Cooper(10), for at this time he stated that the disease occurred chiefly in single women, or in the married who have had no children. He believed it was generally the result of the sympathetic influence of the uterus for the symptoms were more marked at the monthly periods and mentioned that

above all one should learn if the menstrual secretion is regularly performed as regards its time, its quantity, its color, and its duration. Attention was called to the fact that symptoms disappeared with cessation of the uterine excitement or with pregnancy and menopause.

Just one year later (1846) Brodie(11) made an accurate study of the disease and also reported the condition as benign. He was the first to report that the disease was confined to the sexual life of women saying, "I have never known the disease to occur previously to the age of puberty, nor after the middle period of life and if I am not much mistaken it is more common in single than in married women". He mentioned the possibility of the cysts being multiple and also reported that these cysts disappeared spontaneously. The treatment he recommended was evacuation of the fluid contents of the cysts by penetrating it with a grooved needle, but he realized, that no permanent benefits were derived by this method and called attention to recurrence of the lesion unless it was excised. He stated, "Removal of entire breast is under these circumstances, an unjustifiable proceeding, unless the cysts reach inconvenient size

from their bulk". He suggested the name of serocystic tumor.

"I know, in fact, the wonderful sympathy between the ovaries and the breasts", was the statement made by Birkett(12) in 1850, when he named the disease Mazodynia. He reported that the condition occurred before cessation of catamenia, very often early in life and that all women were liable to the disease. The condition usually affected those whose catamenia were frequently irregular both in quantity and quality, was without induration but with or without temporary enlargement of the breasts and took place periodically and contemporaneously with the catamenia or immediately before their appearance.

Velpeau(13) in 1856 called it a physiological engorgement and said, "Pain or change in the shape and size of the mamma, rarely fails to cause anxiety to patients, however slightly it may in reality be. It occurs chiefly in young and especially in unmarried women, and shows itself at the approach of the menstrual period, at the commencement of pregnancy, or on the occasion of any uterine disturbance.

This species of engorgement, which I call physiological, because it depends upon the genital

and sexual functions, and does not, in fact, deserve the name of disease, almost always disappears at the end of a few days or even hours." He described the condition as "Serous Cysts of the Breast" and differentiated it from carcinoma. He recommended iodine injections for cysts exceeding the size of a hazel nut while smaller cysts and those of solid tissue were to be extirpated.(13)

"In 1883, Reclus(14) discussed the condition under the term "Cystic Disease of the Breast", believing that in its multiple form it had hitherto been undescribed. He believed that the "multiple disseminated" and "bilateral affection of cystic production" distinguished the cases observed by him from the simple cysts of the breast described by his predecessors. He called attention to cases of Chronic Cystic Mastitis in which the disease appeared in the remaining half of one breast following a previous excision and then appeared in the remaining breast following the complete removal of the first breast. He called attention to the absence of fluctuation in the large cysts."

"In 1892, Schimmelbusch(6) called attention to the same bilateral affection of the breast as des-

cribed by Reclus(14), but emphasized the variety in which the cysts remained small and in which the epithelial hyperplasia in the acini gave rise to diffuse "shotty" nodules. He called the condition "cystadenoma" and stated that "the pathological process consists in an increase of the acini in the single lobules which show a great similarity to the proliferation which is found in a lactating breast...Epithelial cells pile one upon the other and spread the diameter of the acinus....Through this, when the central lying epithelial cells collapse is the cyst formed."

"Schimmelbusch(6) likened the lobular proliferation to the lactating breast and suggested the possibility of malignant change in one form of Chronic Cystic Mastitis."

König in 1893, at first thought the condition to be of an inflammatory nature and called it "Interstitial Mastitis". He believed the primary process was an inflammation in the connective tissue while the epithelial proliferation was secondary.(8) Later, after having introduced the inflammatory theory, he changed the name to "Chronic Cystic Mastitis".(15)

Bloodgood(4) in 1906, called this condition "Senile Parenchymatous Hypertrophy". He described

the type in which he found cysts in one or both breasts, another which showed one or more smooth-walled cysts, and the adenocystic type in which dilated ducts and acini were filled with proliferating epithelial cells. The later he described as distinctly precancerous.

In 1921, however, he classified the pathology of Chronic Cystic Mastitis into eight groups. The first three groups included single or multiple cysts while the other five groups were made up of those conditions without large cysts. At this time he concluded that Chronic Cystic Mastitis as a whole was not a precancerous lesion.(16)

Semb(5), in 1928, reported a very thorough study of this condition under the title of "Fibro-adenomatosis Cystica Mammae". His divisions were quite similar to that of Bloodgood(16), in which the cystic and adenomatous types were the basis for classification.

In the last decade, as stated by Geschickter (7), in 1934, the experimental interpretation of this disease has been aided by the isolation of hormones from the placenta, from the ovarian follicle and corpus luteum, and from the pituitary. The discovery

of new methods for the biological assay of these hormones has been very beneficial in the study of their relation to the disease process. At this time Geschickter states that the cystic type is related to the hormone of the ovarian follicle and the proliferative type is under stimulation from the hormone secreted by the corpus luteum.

In 1935, Burrows(17) reported the effects of oestrogenic compounds upon the mammae of male mice. This study was made to determine the effects of these hormones upon the mammary gland from which a comparison may be made with the mammary gland of Chronic Cystic Mastitis. Quoting Burrows, "Due to teachings of Sir Lenthal Cheatle and colleagues, "Chronic Cystic Mastitis", is a misnomer, the condition not being essentially of an inflammatory nature. For this reason the term "cystic mastopathy" has been used in this paper, although, possibly, a more explicit and better one might be "oestrogenic mastopathy".

Of the various names suggested for this disease during the past century, "oestrogenic mastopathy" is as descriptive a term as has been given it excepting those used by Cheatle and Cutler.(3)

In the past decade, with the isolation of

the various hormones, especially the ovarian and pituitary hormones, many investigators(3) (17-26) have tried to work out the association of the hormones and the disease process under consideration. By experimental and clinical studies they have tried to analyze the physiological processes which take place and which may be the instigating factors in Chronic Cystic Mastitis. The work of these men will be discussed later in this paper.

THE PHYSIOLOGY OF THE BREAST AND ITS RELATION TO HORMONIC ACTIVITY

"At various stages of their development the mammary glands are subject to stimulation by growth-promoting substances. Thus there are special impulses at birth, puberty, menstruation and pregnancy. It is logical to believe that all these impulses have a common source. Halban(27) in 1905, concluded, without the evidence now in our possession, that the ovary is the seat of origin of hormones responsible for mammary growth and development in the non-pregnant female, and that the placenta is the cause of mammary growth associated with pregnancy."(3)

Horwitz(28) said, "A new concept has come about because the breast has been studied from a viewpoint that it is not a resting organ but an organ having sex rhythm similar to the uterus and, therefore presenting difficult histologic pictures at different stages of the sex cycle. Another helpful aid has been the recent progress in the studies of the sex hormones".

"The amount of involution and evolution which the breast undergoes during its active life is great, no other organ being given to more epithelial

unrest. It is therefore difficult to divide between normal and abnormal".(29)

BIRTH

At birth the child's mammary gland is about 4 or 5 mm. in diameter. The nipple, which at birth is flat, enlarges during the first days of extra-uterine life. During the second week of life, the maximum size, usually 2 to 4 cms. in diameter, is reached after which the size diminishes. Although it has not been proved, it has been stated that the enlargement of the breast in the new-born is greater in girls than in boys.(3)

The mammary gland enlargement is usually followed by a slight secretion. This secretion, known as "witch milk", can be expressed from the nipples about the third or fourth day of extra-uterine life and increases somewhat during the first week but tends to subside or at least to diminish markedly in about two weeks, so that by the end of the first month of extra-uterine life only a small trace, if any, of the secretion persists.(3)

Many theories have been expounded concerning mammary activity observed in the new-born. Halban(27) made a study of the breasts of premature

stillborn infants and was able to demonstrate hyperplasia of the mammary tissues intra utero as early as the eighth or ninth lunar month. He ascribed these changes to hormones from the maternal circulation entering the foetal circulation. Cheatle and Cutler (3) state; "From a review of all the evidence there is little reason to doubt that mammary hyperplasia and secretion of the new-born indicates a response of the breast tissue elements to a hormone".

PUBERTY

"The hypertrophy of the mammary glands at puberty is first noted at about eleven years of age under normal conditions. The first changes are observed in the areola and consist of a swelling of the areola and flattening of the nipple caused by the tension of the skin. The actual enlargement of the breast is due to a hyperplasia of the pericanalicular and periacinous connective tissue and of the duct and acinous epithelium. These changes are followed by an increase in the amount of fat."(3)

Cheatle and Cutler(3) state, "With the onset of puberty the physiological activity of the breast is intimately associated with that of the sexual glands. Horwitz(28) claims that the breast

develops because of stimulation by a hormone from the interstitial cells of the ovary.

That actively functioning ovaries are necessary for the growth and development of the mammary glands can be shown for if ovariectomy is performed before puberty the mammary glands fail to develop. Removal of the ovaries after puberty leads to atrophy of the mammary glands. In women with infantile ovaries, the failure of breast development is further important evidence of the relationship between the ovaries and the breasts.(3) (18)

New development of the breasts was brought about by implantation of ovaries into castrated animals.(27) Werner and Collier(30) were able to bring about activity in the breasts by injections of theelin in women whose ovaries had previously been removed.

We may therefore conclude, as did Nelson(31), that the development of the mammary glands proceeds under the influence of the ovarian hormones. The different degrees of development seen may be due to different degrees of stimulation by oestrone and progestrone.

MENSTRUATION

"The close relationship between the first

menstruation and development of the breasts is best illustrated by those examples in which menstruation begins at an abnormally early age (7 to 8 years). This condition is known as "Menstruatio Precox". In the majority of cases the early manifestations of puberty were associated with corresponding alterations of the mammary glands."(3)

"At every menstrual period the mammary glands are stimulated by hormones that arise in the sexual glands and circulate in the blood, resulting in a transitory swelling of these organs. The stimulus affects both epithelial and connective tissue elements of the breast."(18)

"The cyclic changes that occur in the normal breast associated with menstruation are dependent upon the action of the corpus luteum. This relationship has been established by animal experiments, clinical observation and histological studies."(3) This same conclusion has been reached by Cutler(18), Rodman(25), and Horwitz(28).

MORPHOLOGICAL APPEARANCES AT MENSTRUATION

Rodman in 1930 (29), and again in 1935 (25), brought out the following points following investigations upon the cyclical variations in the histologi-

cal structure of the human breasts in relation to menstruation.

"Somewhere between the menstrual cycles the breast is in its resting stage, probably from the fifth to the fifteenth day after the last menses. At this time the fibrous stroma predominates, the epithelial elements are only ducts and occasionally acini. In old women and obese young women fat is also present. The ducts are lined by two layers of cells; an inner layer of cuboidal or columnar cells with nuclei that are small and stain deeply; and the basal cells that are smaller, and tend to be flattened. As the next menstrual period approaches, the cells become larger until they divide and new ductules are formed branching out from the old ducts like twigs on a tree. The epithelial border around the lumen becomes somewhat jagged and irregular, a change similar to that seen in the glands of the premenstrual endometrium. Meanwhile the surrounding fibrous tissue also softens, undergoing myxomatous and hyaline degeneration so as to allow for the expansion of the ducts. Lobules are thus formed which do not appear in the resting breast. The lining epithelium cells swell, the protoplasm becomes vacuolated and the nucleus is rounder and paler.

Similar changes take place in the cells of the basal layer. Secretion takes place into the ducts and, clinically, in many women the breasts become swollen and tender at this stage. This then, is the premenstrual phase, and about a day or two before the onset of the menstrual flow, involution begins. At this time the epithelium degenerates and is shed into the lumen of the ducts much the same as the superficial layers of the endometrium are cast off during menstruation. Under the microscope, it is seen that the architecture of the lobules has been lost, and they have a curiously jumbled appearance. One now sees degenerate epithelial cells, often varying in size and shape, intermingled with round cells and proliferating fibrous tissue. After the menses are over these degenerate epithelial cells are absorbed. The breast is now in the post-menstrual phase which is short, as in about five days after the menses the breast again enters the resting stage."

This explanation is in agreement with the ideas of other investigators(3) (28) (19), but Horwitz (28), adds that the lymphocytic infiltration in the periacinar connective tissue gave rise to the idea that this was an inflammatory reaction, but lymphocytes

are functional cells containing a lipase and aid in autolysis and are therefore a part of the normal process. He has been upheld in his conclusions by other investigators.

It has been noted that the time relations between the period of high hormone concentration in the circulation, the time of corpus luteum growth, and the period of premenstrual breast activity, is the same(3)

PREGNANCY AND LACTATION.

"During pregnancy the component tissue elements of the breast undergo a marked degree of hypertrophy. In this increased proliferation the epithelial elements undergo the most pronounced change. Outwardly, these changes are marked by an increase in size of the mammary glands that is first noticed about ten weeks after conception. The enlargement of the mammary glands is accompanied by a feeling of fullness, and as the pregnancy progresses the breasts become more pendulous. The nipples become more prominent and the areola undergoes the characteristic changes of pregnancy consisting chiefly of an increase in the amount and extent of pigmentation.

The source and nature of the impulse that

results in the remarkable changes in the mammary glands under the influence of pregnancy has been a subject of extensive investigation and considerable controversy. Numerous theories have been formulated to account for the process of lactation."(3)

"The physiological connection between the ovaries and the mammary glands has been fully established by experimental evidence and clinical observations. While it seems very reasonable to explain the first phase of mammary hypertrophy on the basis of circulating hormones, there are difficulties in explaining how after expulsion of the foetus and its appendages and involution of the uterus the activity of the mammary gland is first stimulated to actual milk production. The development of the mammary glands depends upon the presence of functionally active ovaries, but the production of milk depends upon the abrogation of the ovaries. There is evidence to show that the actively functioning ovary exerts an inhibitory influence on milk secretion and it is when this inhibitory influence is not present that milk secretion occurs. The disappearance of milk secretion under the influence of a new pregnancy is important clinical evidence indicating the introduction of an inhibitory influence to

lactation upon the resumption of ovarian function. These observations emphasize the fact that whereas ovarian function is necessary for the development of the breasts, it is on the cessation of ovarian function that stimulation of the actual production of milk occurs."(3)

MORPHOLOGICAL APPEARANCE AT PREGNANCY AND LACTATION

Rodman(25,29) followed up his contributions on the menstrual phase by the subsequent statement, "If pregnancy intervenes, lactation changes begin. The breast hypertrophies in the same way as it does in the menses, but to a much greater extent. Numerous new acini are now formed and the periductal fibrous tissue is pushed aside, and is no longer distinguishable from the perilobular connective tissue. It is here that the epithelial activity, of course, is at its height. After lactation is over, involution occurs, hyperplasia ceases, secretion is absorbed and the empty acini collapse because of the pressure of the elastic tissue on their walls. Most of the acini disappear at this time but the gland never returns quite to normal virginal state. Lactation hypertrophy, both of the fibrous and the epithelial elements remain to some extent".

MENOPAUSE

"Physiologically, actively functioning ovarian tissue is not as a rule present after menopause, and the ovarian hormones which undoubtedly exert a great influence on breast tissue, are no longer active."(20)

In 1917, Deaver and McFarland(32) pointed to the fact that: "With the advent of the menopause come the final changes to which the mammary gland is subject, and which may be described as senile involution. Presumably they are to be referred to loss of the internal secretion or other factors by which the growth of the mamma was primarily due and its functional potentiality maintained. In general, senile involution is characterized by progressive atrophy and disappearance of the alveolar structure of the parenchyma, progressive destruction of the lobular tissue, increase in the density of the fibrillar tissue, and by a deposit of adipose tissue throughout the breast".

"The microscopic appearances vary according to the past quiescence or activities of the mammary tissue. In the breasts of virgins, and those of women, who have born no children for years before the occur-

rence of the menopause, the changes are comparatively simple. In breasts that have lactated but a short time before, they may be complicated by the presence of incomplete post-lactation involution. In all cases in which mammary tissue is to be examined for morbid processes, the investigator should be informed concerning past and recent activities of the breast, lest he confuse incomplete normal involution with the so-called "abnormal involution."

The changes that characterize senile involution are not difficult to recognize. In some, many, or all of the lobules of the parenchyma, alveoli can be seen whose smaller size and disappearing cells indicate that they are the seat of progressive atrophy. In lobules in which the atrophy has progressed to a marked degree, the intra-lobular connective tissue no longer shows a clear separation from the surrounding inter-lobular stroma or matrix, but more and more blends with it. When the disappearance of the alveoli is complete, the lobules may actually cease to exist because the peri-ductal tissue has so thoroughly blended with the inter-lobular stroma, or may appear as partly differentiated fibrous nodes in a slightly different matricial tissue. Vestiges of alveoli are

sometimes to be found in such fibrillar nodes, appearing as epithelial-lined tubules devoid of a basement membrane and so deformed as not to be easily classed either as alveoli or ducts."(32)

How long involution continues, how regularly it advances, and to what final stage it eventually reaches, appear not to have been definitely followed. It is not improbable that it advances slowly throughout the entire remainder of the subject's life.(32)

THE NERVOUS ELEMENT IN THE FUNCTION OF THE BREAST

The rapid advance made in the knowledge of the functions of the endocrine glands has left in the background the nervous factors which affect the breast.(23)

"Certain evidence, it is true, exists to indicate a relative independence of the breast from the nervous system. Complete severance from its nervous supply by transplantation does not prevent the breast's reaction to the sex hormones or the secretion of milk."(33)

Other experiments have shown that a nervous influence of the breast does exist but these will not be discussed for my main interest is endocrine influence on the breast.

DIAGNOSIS

CLINICAL CONSIDERATIONS

Sir Astley Cooper(34) as early as 1829 noted some of the important clinical features of the disease particularly the intermittant radiating character of the pain, its exacerbations before the menstrual period, and its special frequency in young women of excitable temperament and abnormal menstrual function.

Since Sir Astley Cooper's time many men have recorded the clinical findings of Chronic Cystic Mastitis most of which agree accept for a few symptoms which vary as to the individual case. The following are the usually accepted ones.

"The outstanding symptom is a diffuse aching pain over the whole area of one or both breasts, generally much more marked on one side than the other." (3) The pain is usually confined to the breast or may extend to the arm of the same side.(8) (22) "The pain is often worse at menstruation, but in many cases it is completely unaffected at this period. Sudden jars and excessive use of the arms often lead to accentuation of pain. Tenderness on palpation is sometimes present and may be extremely marked, but

the sign may be absent." Pain, tenderness may disappear spontaneously without obvious reason and when all treatment has failed. Pregnancy and menopause usually bring about termination of all symptoms. The pain may be intermittent or remittent in character.(3) There may be premenstrual fullness or painful swelling or either or both breasts.(28) (18) Cutler (18) stated that, "In many women breast changes associated with menstruation pass unnoticed. Many others complain of pain and tenderness in one or both breasts and at times moderate enlargement is observed". Pain may begin from ten to fifteen days before the menstrual period and diminish markedly or disappear completely with the onset of the period while in others the pain is unaffected by the periods.(18) (22)

The consistency of the breast cannot be successfully established by palpation especially when it is covered by a thick layer of subcutaneous fat. Sometimes by very careful palpation one can detect a diffuse state of fine nodularity of the anterior surface. The gland may feel more solid than normal and this solidity may be uniform or it may be more marked in one place than another.(3) Occasionally single or multiple tumors are palpable. These tumor masses may

on palpation fluctuate or have a cystic feel.(28) This fluctuating spherical tumor is without any peri-cystic inflammatory infiltration.(35) The larger cysts are usually found in the midzone of the breast and not near the nipple or at the periphery.(20) Those breasts which present the "shotty" feeling may have a definite saucer like edge.(26) Axillary glands are practically never enlarged.(3) (8) If a globular tumor is found embedded in the glandular structure of the breast it is usually movable underneath the skin. (32)

There is usually no spontaneous discharge from the nipple, although a thick greenish fluid has sometimes been extracted by artificial means.(3) Hicken, Best and Hunt(36) state that a serous or greenish white discharge may be symptomatic of desquamative epithelial hyperplasia and other conditions but that, "A spontaneous discharge from the nipple of a nonlactating breast is indicative of a physiologic or pathologic abnormality, but it furnishes no clue as to the provocative factor".

HISTOPATHOLOGICAL FINDINGS

Bloodgood's(16) classification of pathological findings in Chronic Cystic Mastitis has been

mentioned before. Cheatle and Cutler(3) have discussed the histopathological findings under the two headings; Mazoplasia and the condition which goes on to the Cystiphorous Desquamative Epithelial Hyperplasia.

In Mazoplasia the epithelium is undergoing desquamative hyperplasia. There may be an increase of the epithelium lining the ducts and acini to two or three rows. Those epithelial cells which have become desquamated are usually desiccated, irregularly shaped and small and stain badly and irregularly. These cells are in various stages of degeneration and are chiefly composed of nuclear fragments. The pericanalicular and periacinous fibrous connective tissue around has undergone hyperplasia and widely separates the acini from each other. Lymphocytes can be seen among the fibers of the connective tissue.(3)

Horwitz(28) stated, "These breasts are characterized by a proliferation of the alveolar and ductal epithelium and by lymphocytic infiltration of interacinar connective tissue. Often there are cysts of varying sizes found which may be lined by flat or papilliferous epithelium", thus suggesting that the one condition was possibly a continuation of the other. Cheatle and Cutler(3), however, seem to be

of a different conclusion by saying, "The desquamative epithelial hyperplasia of mazoplasia never gives rise to cysts". Lewis and Geschickter(20) contribute the following information on the outstanding features of cystic disease. There is a formation of large and small cysts with or without an epithelial lining. One sees an increase in the epithelium lining the duct system with an increase in the entire duct system associated with dilatation of the secondary and terminal tubules. The epithelium is always of the adult type and there is a tendency for it to approach the differentiated columnar type and then liquify or desquamate. The dilated ducts are filled with a material of puttylike consistency, which may be green or gray in color.

The cystiphorous desquamative epithelial hyperplasia of Cheatle and Cutler(3) histologically shows changes which are limited to the smaller and terminal branches. Dilatation, however, does sometimes occur in the large ducts even as far as and including those in the nipple but show no signs of the desquamative process. Their dilatation is attributed to retained collections of fluid. "In the small terminal ducts the desquamative epithelial hyperplasia

begins by the normal cells becoming long and feathery among which can be seen colostrum-like corpuscles in all stages of development. The colostrum-like cells are formed from duct epithelium only. These cells are round and vary markedly in size, but on the whole are large and appear swollen. The cytoplasm is abundant and clear, the nucleus is comparatively small, usually central and as would be expected in a desquamated cell, stains faintly. The mammary ducts are enlarged by this hyperplasia and desquamated colostrum-like cells which collect in the lumen in large numbers and give rise to cysts which always remain small and appear as cysts only in transverse sections of the duct. Occasionally the tips of the feathery cells may coalesce and form continuous arches which include the colostrum-like cells in their meshes. The feathery cells lining the terminal ducts contain lightly stained elongated nuclei and clear cytoplasm. The desquamative epithelial hyperplasia in the larger ducts does not exhibit the formation of feathery cells seen in the terminal ducts. The colostrum-like corpuscles which form in the larger ducts can be seen originating among the upper layers of the lining epithelial cells.*

In the acini, "The first change from the normal epithelium of the acini into the desquamative state is a slight elongation of the cells. In the next stage they become more cuboidal in shape and present a very delicate characteristic appearance. The essential characteristic of those cells is their pallor and they are described as "pale cells". The nuclei are round, hypochromatic and centrally situated. The cytoplasm is homogeneous and perfectly clear. In the next stage these pallid cells increase in number to form two or three rows from which columns of three or four cells may spring and project into the lumen. It is from the upper cells of these columns as well as from the inner layers lining the acini that desquamation occurs. This process and the collection of fluid distend the acini forming small cysts. The desquamated cells become irregular in shape, their nuclei less chromatic and they show all signs of degeneration. The acinous cells which are shed are similar in appearance to those from which they originated. Usually all the acini into which affected terminal ducts lead undergo this change. As the condition advances, the walls which separate neighboring acini disappear and a composite cyst is thus formed. These

early states result in the later formation of the large cysts seen in the breast. They are lined by degenerated and often flattened epithelial cells and their continuity may here and there be interrupted, leaving a bare connective tissue surface of the cyst wall. These cysts are the "blue-dome cysts" of Bloodgood(35)". (3)

The formation of cysts of all variations in size is the end result of the cystiphorous desquamative process. "The pericanalicular connective tissue also may undergo hyperplasia. When it does, lymphocytes may be seen among its fibers or they may be entirely absent over large tracts even where desquamation of epithelium is active. Hyperplasia of this tissue is continuous with that of the periacinous connective tissue which is in the same state of biological activity". (3)

X-RAY, MAMMOGRAPHY, AND TRANSILLUMINATION

Ritus(37) discussed the use of x-ray in the diagnosis of tumors of the breast. He described the picture seen in Cheatle and Cutler's mazoplasia and cystiphorous desquamative epithelial hyperplasia.

"The roentgen picture of mazoplasia is characteristic. The breasts cast a diffuse, hazy

shadow with areas of slightly mottled and increased radiance distributed at irregular intervals. The linear striations of the ducts and acini normally present are entirely absent or nearly so over the main mass of the breast shadow. A few of the linear markings may be visible in the region just below the nipple. There is usually a narrow band of increased radiability along the outer margin of the breast due to fatty tissue deposited in this region. There is no retraction of the nipple, and the skin of the mammary gland is smooth and regular in outline. No glands are present in the axillae.

The roentgen picture of cystoplasia is a very typical one. The linear striations formed by ducts and acini show increased width and density. These striae are more irregular in outline and are separated from one another by a wider space, so that they may appear distributed over practically the entire breast shadow. The striations converge at the apex of the gland and form a broad band extending to the nipple. Scattered irregularly throughout the entire shadow of the mammary gland are multiple trabeculated areas of radiance varying in width from a few millimeters to several centimeters. These areas

are sharply defined, have thin linear borders., are more radiant then the normal breast shadow, and represent the cystic formations. The entire breast appears denser and thicker than usual. Contractions and scarring occur frequently and result in distortion of the breast structures on the roentgenogram. The area of radiance at the posterior aspect of the breast is preserved. These changes are usually bilateral and are similar in character on the two sides.

Large cysts result from the obstruction of a duct or acinus, with consequent dilatation proximal to the point of obstruction. Cysts may be single or multiple and appear as smooth, sharply defined, oval or rounded shadows in the region of acini and ducts. If they do not contain fluid, they are more radiant than the remainder of the breast; if filled with fluid, their density is greater. The linear striae may be compressed, but they are not invaded or destroyed by the pressure of the cysts."

Hicken, Best, and Hunt(36) claim that soft tissue roentgenography fails to depict the identifying characteristics of mammary neoplasms clearly and subsequently show contrast media can be used to great advantage.(36)(38-40)

Mammography as reported by Hicken(39) is a procedure in which contrast fluids are injected directly into the milk ducts and when x-rayed show an accurate pattern of the ductal and secretory system of the mammary gland. Having studied the breast in all its normal physiological states by this method he was then able to interpret pathological findings more accurately. "Mammography finds its greatest usefulness in the study of cystic diseases of the breast. Not only can one determine the size, shape, number, and location of the troublesome cysts but one can also tell whether they are single or multilocular, whether they communicate with the ducts or whether they are isolated or secluded. Likewise one can visualize neoplastic encroachment into the cystic cavities. Such information not only facilitates accurate diagnosis but it aids the surgeon in determining the extent of the diseased process, thus abetting correct treatment". A number of cases were cited where this method of diagnosis was used and very satisfactory result obtained. Various tumors have been visualized preoperatively and correctly diagnosed of which cystic degeneration of the ducts is one.(38) When an abnormal discharge from the nipple is seen

mammography is invaluable in determining the location, extent and identifying characteristics of the pathologic condition producing it.(36)

In addition to mammography Hicken(40) reports on aeromammography. "In spite of their diagnostic value, mammograms unfortunately possess definite limitations. All too frequently, such conditions as obesity, juvenility, inversion of the nipple, advanced involution and subareolar tumors are encountered, which make it impossible to locate the orifices of the lactiferous ducts and hence the thorotrast (contrast media) cannot be introduced. In order to overcome this handicap another form of visualization (termed aeromammography) was employed. It was found that if the mammary tissues were inflated with air, an excellent silhouette of the breast matrix was obtained and that any existing neoplasms were definitely outlined". "A combination of the ductal injection and the insufflation of air produces the most satisfactory visualization patterns of the structures of the breast".(38)

Cheatle and Cutler report that the differential diagnosis between the two types of desquamative epithelial hyperplasia may be made by transillumination because of the translucency of the cysts. Transil-

lumination was also suggested by Bloodgood(41). Transillumination as a diagnostic aid is limited to a small group of pathological conditions and is not an absolute means of diagnosis. Mazoplasia is seen as a diffuse opacity while a cyst containing clear fluid is translucent. Transillumination in conjunction with the clinical history and features enables diagnosis to be made with a greater degree of accuracy.

ABNORMAL PHYSIOLOGY OF CHRONIC CYSTIC MASTITIS

It is not difficult to understand from this brief summary of the divergent views of both clinicians and pathologists, as to the essential nature and underlying pathological process of Chronic Cystic Mastitis and as to the normal physiological function of the breast that one might be affronted with divergent views on the etiology of this condition.

One must, however, keep in mind the work of Bloodgood, Burrows, Cheatle, Cutler, Geschickter, Horwitz, Lewis, Macdonald, Rodman, Taylor and others, who by their observations have concluded that this disease process is an exaggeration of the normal physiological changes in the breast tissue occuring from puberty to the menopause. From these observations conclusions have also been advanced that the ovarian hormones are the etiological factor in this disease.

OESTROGENIC PHASE

EXPERIMENTAL EVIDENCE

Burrows(17) in 1935, studied the effects of oestrogenic compounds upon the mammae of male mice as seen in microscopic sections. His findings were recorded under the following headings.

1. Proliferation of ducts.
2. Dilatation of ducts.
3. Hyperplasia of duct epithelium.
4. Leucocytic infiltration.
5. Increase of periductal fibrous tissue.
6. Alveolar formations.
7. Cancer.

1. Proliferation of Ducts.

In 23 male mice untreated with benzene or any oestrogenic compound revealed but a few cross-sections of ducts in 5 mice. In 57 mammae from male mice which had received applications of benzene only to the skin for prolonged periods, 4 showed more than 10 cross-sections while ducts were seen in 12. In 97 mammae taken from male mice treated with oestrin for more than 55 days ducts were seen in 62 with 56 showing more than 10 ducts.

2. Dilatation of the Ducts.

This condition was never seen in untreated male mice. In 58 mammae of mice treated with oestrin 52 showed dilated ducts. The cystic dilations were formed in part through a general increase in length and diameter of the duct and were filled with a material which stains pink with eosin and appears homogenous. The type of epithelium lining the ducts, not depending upon the degree of tension within the ducts, may be cuboidal or columnar or flattened

epithelium.

3. Hyperplasia of the Epithelium.

This, like dilatation of the ducts, was never seen in the mammae of untreated mice. It was found present in 40% of mice submitted to prolonged treatment with oestrin. Epithelial hyperplasia ensued later in the course of treatment and was less frequent than dilated ducts. A diagnosis of cystic mastopathy was made only when both dilatation of ducts and epithelial hyperplasia were present. The impression was recorded that these two conditions might be in reverse relationship. Epithelial hyperplasia would be seen more often in those which show relatively little dilatation of the ducts, while in the presence of extensive dilatation of ducts there may be but little epithelial hyperplasia.

4. Leucocytic Infiltration.

Leucocytic infiltration may affect some of the ducts only while others in the same section may be free.

5. Increase in Periductal Fibrous Tissue.

"Regarding the frequency with which an increase of the connective-tissue stroma surrounding the mammary ducts may occur under the influence of

oestrin, it is also difficult to speak with confidence. There is little tendency in the mouse, as compared with man toward the formation of fibrous tissue, and I should prefer to leave as an open question the frequency with which an increase of the periductal stroma may take place as a consequency of the administration of oestrin to mice."

6. Benign Adenoma.

Changes in the breast induced by oestrin may be irregular. Some parts of a gland may show advanced changes while other parts may appear almost unaffected. This irregularity has sometimes resulted in the development of local collections of proliferation of ducts which might be regarded as adenomata. Groups of alveolar formations also may appear with prolonged oestrogen treatment. Whether these alveolar formations can be properly termed adenomata or not is difficult to decide. One does not get a substantial development of fibrous tissue in mice which would be comparable with those innocent tumours which occur in women and also rats and dogs.

7. Mammary Cancer.

Out of 116 individuals treated with various oestrogenic compounds only one mouse has developed

cancer. One would not be justified, in the present state of knowledge, that oestrin induces carcinoma in the mamma of mice.

"The administration of oestrin to mice in sufficient amounts over a long enough period is, as our experiments have shown, frequent followed by cystic mastopathy.

The more serious feature of cystic mastopathy from the prognostic standpoint appears to be, not the presence of cysts, but the presence of epithelial hyperplasia. The only sure way of recognizing the presence of cystic mastopathy, when the dilatation of the mammary ducts is insufficient to cause the presence of cysts large enough to be appreciated by palpation or to be seen with the naked eye is by the examination of microscopical sections."

The following points were brought out by Burrows(17) in his discussion of the results of the experiment. Dilatation of the mammary ducts was observed only in mice treated with oestrogenic compounds and with prolonged treatment some degree of epithelial hyperplasia was seen. In other words, cystic mastopathy was seen only in those mice treated with some form of oestrogenic compound. From these

observations he concluded that temporary dilatation of the mammary ducts in a woman prior to the menopause might be regarded as a purely physiological condition, while a persistent dilatation would be presumptive evidence of an abnormal production of oestrogen, or an exaggerated responsiveness to its influence, or a diminution of the natural antagonism to oestrogenic action in that individual. The amount of oestrin in the blood and urine is capable of fairly accurate assay so that one can test an individual for abnormal production or retention of oestrogen. There is needed a test for ascertaining also what may be described as the susceptibility of an individual to the influence of oestrin.

Recognition of the regulation of the oestrous cycle has brought forth the assumption that a natural antagonism, both to the production of oestrin and to its action, exists in the body. As an example Burrows(17) cites, progestin, one of the hormones derived from corpus luteum, which in several respects is an opponent to the activities of oestrin.

The effects of oestrin are reversible, for withholding oestrin, the tissues rapidly return to their former state. This reversibility reveals thera-

peutic possibilities for by adjusting the balance of the hormones would bring cystic mastopathy into the list of preventable diseases.

Lewis and Geschickter(20) studied sections of mammary gland from castrated rabbits and mice after injection of theelin, and theelin and progestin. They also studied the mammary gland of male monkeys and human material which was obtained after several injections of theelin. They concluded that the changes are typical of the microscopic changes encountered in cystic disease, that is, the duct system dilates, there is an increase in the epithelium, and a maturation of the epithelial cells with desquamation. Because the histological changes are so similar to those occurring in cystic disease of the breast and adenosis they feel justified in concluding that these pathological states of the breast are caused by alteration in character, amount or periodic discharge of the ovarian hormones.

Macdonald(42) studied the response of the mammary gland to the ovarian hormones. Seven ovariectomized female rabbits were given daily doses of estrin varying from 25-200 rat units per day for periods varying from 30-187 days.

After about 30 days of estrin injection glandular enlargement three to four times the normal size was seen. The ductal system was ramified extensively, with some widening, particularly toward the main ducts. No acinar growth was seen.

At the end of 80-90 days ducts were definitely increased in caliber. The epithelium was piled up in layers and some smaller ducts were almost plugged with such cells.

Continued treatment with maintained or even increasing daily doses of estrin regression of the glands occurred. Such regression usually began between the 80-100 day of treatment and continued to the resting state of the gland.

From this study Macdonald(42) concluded that ductal distention was greatest when desquamation and early secretion occurred, and was probably due to the mechanical effect rather than any specific influence of estrin on ductal caliber. Long and intensive stimulation with estrin at no time produced a condition which approached the appearance of cystic disease of the breast.

Further study by Macdonald(42) on three ovariectomized does which were given 50 rat units of

theelin and 1 cc. of corpus luteum extract daily for 20-45 days revealed ductal overgrowth with acinar hyperplasia. Ducts were distended by desquamative products and a early secretion of milk.

To one of these animals, after the prescribed course of oestrin and corpus luteum, injections of anterior pituitary extract were given for six days. The gland showed almost full lobular development of late pregnancy and was filled with milk.

Turner and Frank(43) noticed that the daily injection of the estrus hormone in male and female castrated rabbits caused growth of the duct system of these glands but no further growth. They therefore concluded that for further proliferation and formation of lobules characteristic of pregnancy a different agent was necessary. They described this further development when corpus luteum extract was added. This same result was recorded by Parkes.(44)

Parkes and Bellerby(45) and Smith and Smith (46) were able to show that hormones do have antogonistic actions as discussed by Burrows(17) for they were able to inhibit lactation with the administration of the follicular hormone.

Taylor(24) made a study of 261 cases of

breast disease which he classified into three groups.

1. 183 cases showing tender areas of induration or nodularity. Many complained of a temporary premenstrual swelling but none with permanent enlargement or discharge from the nipple.

2. 31 patients with permanent enlargement of the breasts, usually with cyclical pain and swelling, but no discharge from the nipple.

3. 47 cases made up of patients with discharge from the nipple. This group also included many with pain and 6 with hypertrophy.

He also classified these cases as to gynecological history and examination. Those falling into the endocrine field.

1. Breast disease in association with cystic ovaries and menstrual abnormalities. (Anatomical and functional evidence of ovarian disorder).

2. Breast disease in association with cystic ovaries but normal menstruation. (anatomical evidence only of ovarian disorder).

3. Breast disease without evidence of anatomical disease of ovaries, but with menstrual abnormalities. (Functional evidence of ovarian disorder).

   A. Prolonged menstrual cycle, 35 days or longer.

   B. Scanty menstrual flow, 2 days or less.

   C. Excessive or prolonged flow, 8 days or more.

   D. Short menstrual cycle, 21 days or more.

4. Breast disease following hysterectomy. Functional disturbance of retained ovaries).

These patients were studied from the endocrinological phase by five types of hormone analysis.

1. The urinary excretion of estrin in relation to the menstrual cycle.

2. Blood estrin in relation to the menstrual cycle.

3. The urinary excretion of prolan in relation to the menstrual cycle.

4. Serum prolan.

5. Examination of the endometrium.

Taylor(24) concluded from this study that, "Certain minimum activity of the ovary is necessary for development of Chronic Mastitis but no specific hyperfunction or hypofunction of the ovary is at present demonstrable. The results are contrary to hope and expected results from the known proliferative effects of the ovarian hormone on the breast tissue.

Mazer(1) in his study of the relation of the endocrine glands to abnormal breast hyperplasias was able to conclude that the breasts become noticeably enlarged and somewhat tender after several injections of 2000 rat units of oestrin. The glands

returned to normal soon after discontinuation of the hormone. Extensive growth of the duct system in all species was not in proportion to the dose employed. There was also limited or no development of the lobules, however, if projestin is given simultaneously with oestrin and in physiological ratio, lobular development was discernable.

LUTEAL PHASE

EXPERIMENTAL EVIDENCE.

Cutler(18) in 1931 pointed to the fact that, "The corpus luteum of menstruation and the corpus luteum of pregnancy are responsible for the normal physiologic hypertrophy of the mammary glands. During the state of proliferation of the corpus luteum (the premenstrual stage) the epithelial hyperplasia is most marked and hyperplasia of the breast elements has been produced experimentally in animals by injection of corpus luteum.

Lewis and Geschickter(20) in 1934 followed up their experiments with the conclusion that experimental results produced by progestin are more difficult to demonstrate because the active extracts are not easily obtained and the progestin effects depend upon the synergistic effect of theelin. Theelin alone

produces ductal proliferation typical of the microscopic changes encountered in cystic disease. Mammary glands of castrated rabbits after daily injections of theelin and progestin showed marked proliferation of lobular epithelium resulting in the formation of numerous acini. The tissue formed as the result of the action of progestin was histologically much like that encountered in adenosis. These results agree with those obtained by Turner and Frank(43) in 1931.

Macdonald(42) in 1936 experimented with the mammary glands and their response to ovarian hormones. Three rabbits received daily injections of 1 cc. of corpus luteum extract for periods of 10, 54, and 81 days. A study of the mammae showed no significant changes had taken place. However, with the simultaneous injection of theelin and corpus luteum extract, both ductal overgrowth and acinar hyperplasia were demonstrated.

"Clinical, pathological and experimental evidence clearly indicates that excessive epithelial and connective tissue hyperplasia giving rise to diffuse generalized pain and nodularity in the breasts in relation to menstruation may be due to excessive corpus luteum stimulation", was stated by Cutler(18)

in 1931. "In patients suffering from 'painful breasts' the corpus luteum dominates the ovarian metabolism and by inducing an excessive epithelial and connective tissue hyperplasia causes diffuse pain and generalized nodularity of the breasts. At the same time the over-active corpus luteum suppresses ovulation and exerts an estrus-inhibiting influence leading to a hypo-function of the follicular and interstitial elements of the ovary, as indicated by the short and scanty menstrual periods in these cases."

Administration of corpus luteum extract actually increased the pain in some cases while the attempt to restore normal balance by the administration of ovarian residue was met with favorable results. (18)

Mazer(1) obtained similar results to those of Turner and Frank(43) and Lewis and Geschickter(20) in that no effect was produced in either the ducts or lobules or the nonlactating breast by the injections of corpus luteum extract alone but simultaneous administrations of theelin and corpus luteum extract evoked ductal and acinar growth.

PITUITARY PHASE

"The pivotal role of the anterior pituitary

gland in the initiation and maintenance of lactation after the breasts have been prepared by estrin and progestin is no longer debatable", was the statement made by Mazer(1). His observations are similar to those made by Corner(47) who in addition described a definite proliferation of the mammary gland in spayed virgin rabbits following two weeks administration of extracts of whole sheep's hypophysis. "This observation, according to Mazer(1), is of utmost clinical importance. It shows that at least in one species anterior pituitary extracts can produce acinar growth which is held by many to be the exclusive property of the corpus luteum hormone, progestin. This action of the anterior pituitary lobe is however predicted on the pre-existing estrin influence on the breast structure, since it cannot be duplicated in immature rabbits whose mammary glands had not received the stimulus of estrin."

If the responsiveness of the human adult breast under certain circumstances be similar to that of the rabbit, the altered pituitary function current during premature decline of sexual life may be a factor in the production of the abnormal breast hyperplasia often seen in these patients.(1)

An observation made by Rodman(25) resulted in the statement that, "In all probability, a hormone from the anterior pituitary body controls the secretion from the graafian follicle and the corpus luteum of the ovary, which in turn controls the growth of the breast tissue".

Evans and Simpson(48) noted that the injection of anterior pituitary into infantile animals was followed by mammary development before corpora lutea appeared in the ovaries. They also obtained hyperplasia of the mammary glands in the infantile and adult rats by injection of anterior pituitary which they thought might be affected by way of the ovary. Their conclusion was that the exact role of the corpus luteum in mammary growth and lactation was an undetermined question.

Nelson and Smelser(49) in 1933 revealed that lactation might be induced in the absence of any luteal influence which was followed by a statement by Nelson (31) in 1936 to the effect that although initiation and maintenance of lactation depended upon the presence of the anterior hypophysis the ovarian hormones were antagonistic to the extent that they inhibited the influence of the anterior pituitary and prevented

lactation. Allen and Wiles(50) pointed to the fact that the partial development or stimulation of the mammary gland by ovarian hormones is necessary before the anterior pituitary hormone can be effective. In 1929, Parkes(51) obtained full mammary development in rabbits by injections of alkaline extracts of the anterior pituitary. He attributed this, however, to the resulting prolongation of the luteal activity.

CLINICAL OBSERVATIONS

PELVIC TUMOURS

Taylor(22) observed that small cysts may develop in the retained ovaries after hysterectomy. This fact has been recognized clinically and has been demonstrated on certain animals. Improvement in breast symptoms when these retained ovaries were treated by x-ray was most striking. This observation was repeated by Taylor(24) when he reported that, "From 21 cases observed at operation by the author and from reports of pelvic pathology of 47 further cases operated upon by other surgeons, one can find evidence of a relatively high incidence of cystic disease of the ovary. The ovary with multiple small cysts was a much commoner finding than the larger cysts, particular in cases with breast pain and

diminished menstruation". He mentioned the report of three experimenters who found an increased estrin excretion after hysterectomy, perhaps due to the failure of the endometrium to utilize its quota of hormone.

Taylor(21) in 1933 said, "Since in many cases the symptoms are greatly intensified just before the onset of the menstrual period it is not surprising that attention has been directed to the uterus and ovaries in the search for possible causes", and subsequently cites two cases which reflect this theory.

Case 1. B. M.

"The first patient was a young white woman of 26 years, married but divorced, without pregnancies. For six months before her first visit to the clinic the patient has suffered from a variable but continuous tenderness and a progressive increase in size of the right breast and for two months these symptoms had been noted in the left breast also. An exacerbation of the pain occurred during the ten premenstrual days, during which time the discomfort was so severe as to make sleep difficult and little relief was obtained for several days after the periods started.

Examination showed a young well-nourished blonde woman five feet five inches in height, 146 pounds in weight. Both breasts were of medium size and erect, the right considerably larger than the left. The breasts were tense with dilated blue veins coursing over their surfaces and definite striae in the skin like those observable in pregnancy. On each side there were exquisitely tender areas of induration, localized especially in the upper outer quandrants.

Inquiry disclosed no gynecological symptoms except a recent change in the menstrual flow which although always irregular had recently decreased until each period was of barely two days' duration. Vaginal examination revealed, however a cystic mass filling the culdesac, measuring 15 cm. in diameter, and lying posterior to a normal sized uterus. A diagnosis of ovarian cyst was made and the patient advised to have it removed with the assurance that her breast symptoms would probably improve thereafter.

The patient decided to have her operation in another institution. Her surgeon reported by letter that he had performed a bilateral salpingectomy and partial left oophorectomy for bilateral hydrosalpinx and left ovarian cyst. Two months afterward the

patient returned to the breast clinic and reported that her breast pain had been reduced to a little discomfort before her periods and that her chest circumference had diminished two inches. Examination revealed nolonger any tenderness, little difference in size between the two breasts, a disappearance of the striae and a general softening of the breast tissue. A year later further improvement was to be noted although the periods had remained very scant and some premenstrual tenderness was still present."

Case 2. E. B.

"The second patient was a colored woman of 37 years, formerly married but now separated from her husband, with a history of one miscarriage 16 years previously. Three years before admission to the breast clinic, the patient had undergone a supravaginal hysterectomy and left salpingo-oophorectomy for fibromyoma and ovarian cyst. Since the time of the patient's miscarriage there had been a slight persistent milky discharge but no pain until one year ago, (two years after the hysterectomy) when the right breast became markedly swollen and exquisitely tender. More recently similar but less sever symptoms had developed in the left breast also. Examination of the breasts

showed them to be of medium size, tense, and erect, the right considerably larger than the left, with circumscribed areas of induration in the outer quadrants, so tender as to make palpation almost unbearable to the patient. Pelvic examination disclosed a small cervix, a small mass in the right fornix regarded as a cystic ovary and a vaginal mucosa that showed no evidence of atrophy.

Two full treatments of high voltage x-ray were ordered given to the right pelvis but the patient submitted to only one of these. Within four weeks the pain had practically disappeared and after two months the breasts were soft and nearly equal in size but the secretion from the nipples had continued. At the end of eleven months the hot flashes which had at first been troublesome began to disappear and a slight return of the breast pain developed. At present, nearly three years after her treatment, the patient is practically free from symptoms and the breasts are essentially normal."

"The most obvious explanation of the breast changes in these cases is that they result from some abnormal stimulation, perhaps hormonic in character, dependent in each case upon a cystic ovary."

Lewis(19) observed a case in which the patient, a white female, age two, had begun to menstruate at three months. Shortly afterwards both pubic and axillary hair appeared. The breasts developed as large as those of a normal developed girl of thirteen or fourteen. An exploratory laparotomy revealed an ovarian cyst on the right 5 cm. in diameter.

X-RAY

Taylor(24) studied the effect of radiation of the ovaries in cases of chronic cystic mastitis. In 12 cases the effect of pelvic x-ray, and in 3 in which radium was used on the uterus immediate evidence of improvement in the pain and swelling and the nodularity of the breast tissue was observed. In 6 cases in which the radiation dosage was sufficient completely to suppress the ovarian function, permanent improvement was noted. In 2 cases in which x-ray of the pelvis was given, the hormone excretion was studied for 3 months after treatment by weekly examination of specimens. In both, the improvement in the breast symptoms corresponded with a decided drop in the rate of estrin excretion and the appearance of prolan in the urine.

The use of x-ray can be made in only certain

cases as brought out by Taylor(22).

1. Women over 45.
2. Those over 40 with menopause already suggested by irregular periods.
3. Women with uterus removed.

Improvement was so striking when x-ray was used that Taylor(22) suggested its therapeutic use in cases of ovarian dysfunction and chronic cystic mastitis.

PREGNANCY AND LACTATION AND MENOPAUSE.

Lewis and Geschickter(20) (52) have observed that symptoms rarely persist during pregnancy and tend to disappear with lactation and menopause.

GENERAL DISCUSSION

Many theories have been presented by various experimenters as to the nature of the disease process and they offer evidence to support their views.

Lewis and Geschiskter(20) noted that the cystic disease disappeared during pregnancy and adenosis rarely persisted thru pregnancy. This evidence was given to support a functional disorder. They offered the conclusion that the pathology of chronic cystic mastitis was of two types related to the two separate functions of the breast, and these in turn to the two separate influences of the ovarian hormones

theelin and progestin which in order to instigate pathology are altered in character, amount or periodicity of discharge.

An important contribution was made by Horwitz(28). He said, "The uterus shows failure of pregnancy by casting off its decidua in the menstrual flow, but the breast cannot get rid of its secretion and its desquamated epithelial cells except through absorption, either because the coagulation of the secretion or the keratinized cells or the hypertrophy of the ductal epithelium obstructs the lumin of the ducts.

If the breast is to return to its resting phase completely there must be a balance between secretion and absorption, a condition which is under the control of the internal secretions of the anterior pituitary gland and the ovary.

If the luteal phase of the ovarian secretion is prolonged there will be overstimulation of the breast with consequent increased epithelization and hypersecretion. During the intermenstrual phase, the breast will not be able to regress to the resting phase and the result will be distortion of the acini with desquamated cells and unabsorbed secretion, with

hyperplastic interacinar connective tissue infiltered with lymphocytes. With the new luteal phase coming on with the next premenstrual period more stimulation is applied and further distention of the acini and ducts will occur with incomplete return to physiological normal."

All observers of this condition are in agreement that one should have complete data of the menses and sexual life of the patient before attempting treatment.

TREATMENT

According to Dahl-Iversen(53), "The conservative management of cystic mastopathia finds a new basis in recent observations on the favorable influence of oestrin. Under this treatment the symptoms either disappear or are considerably relieved, and examination shows that the signs are diminished or almost absent, the result being especially good in early cases".

In 1935, 22 cases of cystic mastopathia were treated with oestrin and considerable recovery was observed in 18. In 2 patients, both between 20 and 30, the local and general condition was aggravated, and in 2 cases there was no effect.(53)

"In the light of our present experience we should advise a dosage of 2000-4000 mouse units daily by mouth or 10,000-20,000 mouse units once a week intragluteally. The course of treatment should last 3-6 months, and in some cases should be continued longer, with pauses. The idea that the remedy is more than symptomatic is supported by the evidence of biopsis which hystologically suggested the regressive changes of menopause or that of breast subjected to energetic x-ray treatment.

The treatment seems applicable especially to cystic mastopathia in young women in the hope of avoiding operation.

Surgery should be regarded as inadvisable unless oestrin proves of no avail or there is some doubtful change in the clinical picture. If operation is decided upon, partial exterpation finds favor if the process is clinically localized."(53)

Horwitz(28) mentions that ovarian residue is useless in painful breasts but folliculin and anterior pituitary hormone injections may help. X-ray radiation over the ovaries has been met with good results.

X-ray has also been suggested by Taylor(22) who puts certain restrictions upon its use. Women over 45 years of age or those over 40 with menopause already suggested by irregular periods or those with previous hysterectomy are likely subjects for this therapy. Definite improvement in breast symptoms has followed a single high voltage treatment of 200 r units without the production of distressing vasomotor symptoms. He suggested that a trial of the more potent modern preparations of folliculin and anterior pituitary hormones is indicated in cases in which

breast symptoms are associated with disturbed menstruations.

Cutler(18) showed that ovarian residue relieved the condition whereas whole ovarian substance and particularly corpus luteum usually accentuated the pain and tenderness. Ovarian residue given 5 grains daily to 5 grains three times a day showed definite response. Ovarian residue to be given 15 days before the onset of the periods and stop with their onset. No standard dose can be formulated for all patients.

Cheatle and Cutler(3) suggested excision of single cysts with removal of the entire gland in case of multiple cysts for they claim that about 20 per cent. of all carcinomata of the breast begin within the lesions of the cystiphorous state.

Geschickter(26) in 1938 stated that the early stage of Chronic Cystic Mastitis responds to estrin as well as the proliferative stage. The dosage employed most successfully was; 10,000 international units intramuscularly twice weekly. The dose is not given during the menstrual period and is gradually tapered off after two months so that during the third month one injection a week is given. During the

fourth month only two injections are given and finally only one injection a month premenstrually is given. In the form of the disease characterized by large blue-dome cysts, large doses, 10,000 to 20,000 international units, twice weekly over a period of several months has occasionally been effective.

Many men now agree that the breast need not be sacrificed surgically in Chronic Cystic Mastitis.

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